Claims 52 and 54-62 as submitted on November 19, 2010 are pending

Alleged rejections under 35 U.S.C. § 103

The Advisory Actions mailed December 2 and 22, 2010 as well as February 23, 2011 indicate the maintenance of rejections under 35 U.S.C. § 103(a) based on Chapple et al. and Asato et al., as a pair or in further combination with additional cited documents.

The remaining rejections assert that Chapple et al. (2003) provides motivation and a reasonable expectation of success in treating P23H opsin mutation in a human patient with 9-*cis*-retinal and also assert that Asato et al. (1978) indicates functional equivalence between 9-*cis*-retinal and 9-*cis*-10-F-retinal (see Adv. Actions mailed Dec. 2, 2010 and Feb. 23, 2011). Mainly based on these assertions, the claims were alleged to be obvious. But these assertions and allegation fail to meet the requirements for a *prima facie* case of obviousness.

I. Failure to Follow the Preponderence of Evidence Standard

The Office requires that the "preponderance of the evidence" test be the patentability standard applied in the instant application. According to this standard, a rejection of a claim is proper only if the evidence of record indicates that it is more likely than not that the claim is unpatentable (see MPEP 706 I). In other words, if the evidence for and against patentability is equal (or "50/50"), a rejection is improper. The Federal Circuit has applied this standard in rejections under 35 U.S.C. § 103(a)[1]. The standard requires an allegation of obviousness to be based on evidence which, as a whole, indicates that the legal conclusion to be proved (i.e. establishment of a *prima facie* case of obviousness) is more likely than not.

But this standard has not been followed in the remaining rejections. This failure is seen in the evidence regarding selection and use of 9-*cis*-10-F-retinal as featured in the claimed methods to treat a human disease condition caused by a P23H mutation in opsin protein. The evidence of record includes the following:

i) 9-*cis*-retinal binds P23H mutant opsin protein in an *in vitro* monkey cell based assay, and

ii) the human disease condition to be treated by the claimed methods afflicts human subjects despite the *in vivo* presence of endogenous 11-*cis*-retinal.

9-*cis*-10-F-retinal, 9-*cis*-retinal, and 11-*cis*-retinal are all analogs of each other. Applicants respectfully submit that the above evidence, as a whole, fails to indicate that it would have been more likely than not, at the time of the invention, for a skilled person to find it obvious to use 9-*cis*-10-F-retinal in the claimed methods to treat the human disease condition due to the P23H mutation in opsin.

The remaining rejections and the Advisory Action mailed February 23, 2011 assert in part that the use of 9-*cis*-10-F-retinal would have been obvious because it and 9-*cis*-retinal are disclosed by Asato et al. (1978) as able

[1] See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992) and the Legal Concept of *Prima Facie* Obviousness at MPEP 2142.

to bind to non-mutant opsin protein. But this assertion ignores evidence that 11-*cis*-retinal ***also binds non-mutant opsin protein***[2]. The arbitrary selection of only the evidence regarding 9-*cis*-retinal, while ignoring the evidence regarding 11-*cis*-retinal, is a clear failure to follow the preponderance of the evidence standard.

Moreover, a skilled person would give greater weight to the evidence regarding how the *in vivo* presence of endogenous 11-*cis*-retinal fails to alter the same P23H mutant opsin mediated human disease condition to be treated by the claimed methods. This *in vivo* information is clearly more relevant to the pending claims than the evidence regarding the *in vitro* behavior of 9-*cis*-retinal in monkey cells expressing P23H mutant opsin.

Therefore, proper consideration of the evidence as a whole does not support a contention that the presence of obviousness is more likely than not. The ability to bind non-mutant opsin protein, based upon Asato et al. (1978), provides no information regarding the issue of using 9-*cis*-10-F-retinal in the claimed treatment methods. Binding to non-mutant opsin is not relevant because the ability to bind non-mutant opsin is present in 9-*cis*-retinal, alleged in the remaining rejections to work in the treatment of the disease, and in 11-*cis*-retinal which is known to be present, but ineffectual, in human subjects with the disease to be treated by the pending claims. Additionally, the 11-*cis*-retinal evidence is more relevant to the pending claims because the same *in vivo* condition is present. Thus even with inclusion of Asato et al. (1978), there is a failure to meet the "more likely than not" standard required for a *prima facie* case of obviousness. For this reason alone, the remaining rejections are misplaced and may be properly withdrawn.

II. Improper Reliance on Factually Unsupported Subjective Evidence

The Office has set forth standards for the consideration of objective evidence, including the requirement that evidence supporting patentability must be weighed against evidence in favor of a *prima facie* case (see for example, MPEP 716.01(d)). But the remaining rejections rely upon subjective evidence to assert a *prima facie* case without proper recognition that the subjective evidence is unsupported by objective supporting patentability.

The Advisory Action mailed February 23, 2011 asserts in part that the claimed invention is obvious because Chapple et al. (2003) provides an opinion that "data suggest that retinoids may be used as 'chemical' chaperones that can stabilize the folding of mutant opsins shifting the equilibrium away from aggregation and towards functional protein." But this opinion statement refers to objective "data" by Saliba et al.[3] regarding 9-*cis*-retinal and by Syed et al.[4], and Applicants respectfully submit that the facts of Saliba et al. do not support the opinion statement.

---

[2] This established fact is a part of the understanding of vertebrate vision, including human vision.

[3] Of record in the instant application as indicated in the initialed Information Disclosure Statement mailed by the Office on January 27, 2009. The citation is Saliba et al., "The Cellular Fate of Mutant Rhodopsin: Quality Control, Degradation and Aggresome Formation" J. Cell Sci. (2002) vol. 115, pp. 2907-2918.

[4] This is Reference 24 in Chapple et al. (2003), which has incomplete bibliographic information. The statement citing to Syed et al. states "[a]ddition of a modified retinoid, 11-*cis*-7-ring-retinal, has also been shown to improve the folding of rhodopsin containing the P23H mutation." There is no comment regarding effect on aggregation.

The key point in the opinion statement is that "retinoids [such as 9-*cis*-retinal] can stabilize the folding of mutant opsins shifting the equilibrium away from aggregation and towards functional protein." But the facts in Saliba et al. clearly state that "incubation of 9-cis-retinal did not lead to a significant decrease in the formation of [P23H mutant opsin] aggresomes over the period of the treatment time" (see page 2914 of Saliba et al.). This clearly does not support the concept of "shifting the equilibrium away from aggregation" as alleged in the opinion statement.

Saliba et al. further state that "in the presence of [P23H] mutant protein aggresomes, the normal wild-type [opsin] protein can be recruited to the inclusions" (see page 2915, left column, first paragraph, last sentence; pages 2910-2911; and Figure 5 on page 2912). The factual observation of recruitment of wildtype opsin to aggresomes also does not support the concept of "shifting the equilibrium away from aggregation and towards functional protein" as alleged in the opinion statement.

Applicants respectfully submit that it is improper to rely upon the opinion statement by Chapple et al. (2003) when it is clearly not supported by the objective evidence of Saliba et al. It takes willful blindness to focus on an opinion statement, however favorable to a *prima facie* case, that is contrary to objective facts of record. And even assuming for the sake of argument that the facts of Syed et al. were supportive of the opinion statement, they cannot change the conclusion that the facts of Saliba et al. do not. In such a case, there is no preponderance of evidence to support the opinion statement, and so the statement cannot be considered more likely than not to be correct. Therefore, the opinion statement cannot support a case of obviousness, and the remaining rejections should be withdrawn.

III. Failure to Accord Weight to Evidence in Support of an Expectation of Success Not Present in the Cited Documents

The above discussion of evidence by Saliba et al. is in contrast to evidence in the instant application in support of an expectation of success for the claimed methods. For example, the instant application discloses that human cells expressing P23H mutant opsin were observed to be rescued with a retinoid and with predominant localization in a non-aggregated, "diffuse pattern with significantly greater staining at the cell surface similar to … wild-type opsin, which are predominantly at the plasma membrane" (see page 25, paragraph [0084] of the instant application).

Thus while Saliba et al. reports no significant decrease in the formation of aggresomes, the instant application is supported by data showing non-aggregated P23H mutant opsin in human cells. A skilled person would recognize this information from the instant application for combination with Saliba et al.'s statement that "in the presence of [P23H] mutant protein aggresomes, the normal wild-type [opsin] protein can be recruited to the inclusions" (see page 2915, left column, first paragraph, last sentence; pages 2910-2911; and Figure 5 on page

2912). The combination leads, in part, to the expectation that normal wild-type opsin protein would NOT be deleteriously recruited to aggresomes.

A further comparison of Saliba et al. to the instant invention indicates additional evidence of unexpected factors to support an expectation of success. Saliba et al. report the targeting of P23H mutant opsin to a monkey cell's plasma membrane without indication of whether the P23H mutant opsin was properly folded or glycosylated. This is in contrast to the instant invention, which includes evidence that a retinoid rescued P23H opsin in human cells had a glycosylation pattern similar to normal, non-P23H opsin (see page 24, paragraph [0079] of the instant application).

Saliba et al. also report the use of tunicamycin to inhibit glycosylation of the P23H mutant opsin (see pages 2913 to 2914 and Figure 9 on page 2915). The inhibition resulted in no change to the formation of aggresomes, but an accumulation of unglycosylated P23H mutant protein in the endoplasmic reticulum (ER) is reported. Saliba et al. comment that the "data show that the major effect of inhibiting N-linked glycosylation in COS-7 cells is to prevent the degradation of the mutant protein and lead to its retention in the ER" (see page 2916, left column). But if the glycosylated form is more suited for degradation of the P23H mutant opsin, the person of ordinary skill in the art would not have expected that glycosylation aided by a retinoid (as disclosed in the instant application) would help P23H folding and avoid degradation.

None of the above evidence in support of an advance over the cited documents has been afforded full consideration during prosecution of the instant application.

IV. Improper Reliance on "Obvious to Try"

The remaining rejections rely upon an erroneous "obvious to try" rationale while also failing to consider the entirety of the evidence, which includes information regarding "cytoplasmic chaperones" and "chemical chaperones" in the cited documents.

It is well settled law that obviousness cannot be based upon an impermissible "obvious to try" rationale as the motivation.[5] One clear example of impermissible "obvious to try" is where a skilled person might "explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.[6] The Supreme Court expressed the same idea in *KSR* by requiring that identified solutions be

[5] *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988).
[6] *Ibid.* at 903.

"predictable"[7] and by indicating that non-obviousness is present where an "improvement is more than the predictable use of prior art elements according to their established functions."[8]

But as evident in the Advisory Action mailed December 2, 2010, the remaining rejections rely heavily upon page 13 of Chapple et al. (2003) to allege both motivation and a reasonable expectation of success in using molecular chaperones as a potential human therapy. The rejections erroneously apply one portion of that passage while the remaining portion only rises to the impermissible "obvious to try" standard. This is shown by the following statements from, and analysis of, disclosures in the cited documents and remarks from that Advisory Action:

The following numbered statements are from page 13 in Chapple et al. in the section entitled "Improving rhodopsin folding; molecular chaperones and potential therapy"	
Regarding "cytoplasmic chaperones" (with HSJ1b as the only example)	Regarding "chemical chaperones" (with 9-*cis*-retinal as one example)
1---"HSJ1b is localized to the cytoplasmic face of the endoplasmic reticulum [(ER)] and will thus encounter cytoplasmic domains of rhodopsin *in vivo*." 2---"the [HSJ1b] chaperone caused wild type rhodopsin to be retained in the ER and increased the incidence of aggresome formation for both wild type and P23H rhodopsin…" 3---"These data provide evidence that cytoplasmic chaperones can influence the folding and processing of rhodopsin." 4---"Understanding the specialized chaperone networks within photoreceptors will be essential to exploit the potential of cellular chaperone machines to manipulate the folding of normal and mutant rhodopsin."	5---"In addition to manipulating molecular chaperones, there is the potential to manipulate protein folding by 'chemical chaperones' or stabilize protein structures using ligands." 6---"the folding of mutant rhodopsin has been improved by the natural ligand retinoids." 7---"addition of 9-*cis*-retinal to cultures expressing P23H mutant opsin improves the amount of opsin that reaches the plasma membrane, whilst having no effect on K296E [another misfolding] mutant opsin." 8---"These data suggest that retinoids may be used as 'chemical' chaperones that can stabilize the folding of mutant opsins…."

The remaining rejections assert that above statements 1 and 3 "address[] that cytoplasmic chaperones can influence the folding and processing of rhodopsin in both wild type and P23H rhodopsin" and that "Chapple addresses that chaperones can be utilized to manipulate the folding of normal (wild type) and

[7] *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007).
[8] *Ibid. at* 417; see also *Proctor & Gamble v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989, 996-97 (Fed. Cir. 2009) and *In re Kubin*, 561 F.3d 1352, 1359-60 (Fed. Cir. 2009)..

mutant rhodopsin *with a reasonable expectation of success*" (emphasis added). These assertions selectively interpret the disclosure because they wholly ignore statement 2, which clearly describes how the only disclosed "cytoplasmic chaperone" had a **negative effect** on the folding of wildtype rhodopsin while **not improving** the misfolding of the P23H rhodopsin. With inclusion of all facts, the assertions are wrong in arguing that because a "cytoplasmic chaperone" *negatively* influences the folding of both wildtype and P23H rhodopsin, it is reasonable to expect that a "chemical chaperone" will *positively* influence the folding of both. This is simply illogical or the result of speculation. In either case, the assertions are based upon the selective failure to consider the entirety of the evidence.

Instead, and consistent with above statement 4, the skilled person cannot readily expect all chaperones as having a positive effect on wildtype rhodopsin folding or on the misfolding of P23H rhodopsin. To the contrary, statement 4 suggests experimentation in order to "understand" how "to manipulate the folding of normal and mutant rhodopsin. Thus the disclosure regarding "cytoplasmic chaperone" is an impermissible "obvious to try" level of motivation[9], such as where a skilled person might "explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it[10].

And while statements 5 thru 8 disclose the use of "chemical chaperones," the statements provide little guidance regarding additional retinoids to improve folding of mutant opsins. The use of 'chemical chaperones' or ligands is a type of "new technology or general approach," while using retinoids is "general guidance as to the particular form of the claimed invention or how to achieve it.[11]" Multiple different opsin mutations (T17M, P23H, and K296E on page 13 of Chapple et al.) are discussed while the functionality of the listed retinoids (11-*cis*-retinal, 9-*cis*-retinal, 11-*cis*-7-ring-retinal, and vitamin A on page 13 of Chapple et al.) is unclear.

Additionally, the remaining rejections erroneously assert a reasonable expectation of success by relying on the last two paragraphs on page 13 in Chapple et al. (2003). The incorrect assertion is to test vitamin A, or another retinoid, in a modified "clinical trial" (by Berson et al.[12]) of "patients with misfolding mutations in rhodopsin [because] the clinical outcomes might have been even better." The error is clear from the Berson et al. report of the "clinical trial", where they state that

---

[9] *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988).

[10] *Ibid.* at 903; The Supreme Court expressed the same idea in *KSR* (550 U.S. 398, 421 (2007)) by requiring that identified solutions be "predictable" and by indicating that non-obviousness is present where an "improvement is more than the predictable use of prior art elements according to their established functions." *Ibid. at* 417. See also *Proctor & Gamble*, 566 F.3d 989, 996-97 (Fed. Cir. 2009) and *In re Kubin*, 561 F.3d 1352, 1359-60 (Fed. Cir. 2009).

[11] *In re O'Farrell*, 853 F.2d 903 (Fed. Cir. 1988).

[12] Referring to Reference 25, as cited in Chapple et al., which is Berson et al. (*Arch. Opthalmol.*, 111:1456-1459, 1993), of record in the instant application (see signed form SB/08a of October 15, 2009).

> "[w]e must also emphasize that our conclusions are based on group averages, and therefore we cannot provide assurance that a specific patient will benefit from this treatment. We found no evidence that the beneficial effect of vitamin A was confined to one or another genetic type. It remains to be established whether vitamin A supplementation will have the same effect on retinal function in all groups of patients with recently discovered subtypes of retinitis pigmentosa defined through moleculr genetic analysis."[13].

The table at the top of page 766 in Berson et al. shows the genetic types to include 76[14] "dominant" subjects with "recessive", "X-linked", "isolate", and "undetermined" types also listed. As previously acknowledged by the Office, the autosomal dominant P23H opsin mutation in the claims is one possible "dominant" genetic type, and so "dominant" subjects in Berson et al. may include this mutation. But there is no information as to how many of the "dominant" subjects in Berson et al. have the P23H opsin mutation and whether any of them displayed a positive beneficial effect with vitamin A.

This lack of a positive benefit with vitamin A in connection to the P23H opsin mutation shows a lack of support for the remaining rejections. This is analogous to the negative results discussed in Chapple et al. with respect to "cytoplasmic chaperones." So while the remaining rejections allege a generalized reasonable expectation of success in using vitamin A or another retinoid to treat P23H subjects, the assertion is only possible with improper exclusion of the underlying data from Berson et al. If the data is properly included, the allegation is clearly speculation because it is not supported by the underlying objective facts. Reliance on Chapple et al.'s remark regarding "clinical outcomes [that] *might have been* even better" (emphasis added) is acceptable only with proper recognition that it reflects an insufficient suggestion to try where Berson et al.'s data provides no expectation of a successful result.

And if the assertions in the rejections are limited to expectations based on using 9-*cis*-retinal to treat P23H in human subjects, the Office turns to Asato et al. (1978) for its disclosure regarding 9-*cis*-10-F-retinal. This is needed to avoid an improper *per se* test of obviousness based on structural homology alone[15]. Following the Supreme Court in *KSR*, the Federal Circuit in *Takeda* confirmed that a *prima facie* case includes "a showing that the 'prior art would have suggested making the specific molecular modifications

[13] See pages 770-771, bridging paragraph.
[14] 76 subjects is the sum of Group A subjects: 45 in the All Randomized Patients and 31 in the Higher-Amplitude Cohort.
[15] It is well settled that "obviousness requires a suggestion of all limitations in a claim." See *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003), citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974).

necessary to achieve the claimed invention.'[16]" even where "[a] known compound may suggest its homolog, analog, or isomer…."[17] While the motivation is not required to be explicit in the art, the lack of expectation in achieving the claimed invention, or reliance upon a property different from that needed in the claimed invention, is not sufficient motivation.

The remaining rejections assert that Asato et al. (1978) indicates functional equivalence between 9-*cis*-retinal and 9-*cis*-10-F-retinal sufficient to motivate modifying Chapple et al. (2003) by replacing 9-*cis*-retinal with 9-*cis*-10-F-retinal in treating P23H mutant opsin in human subjects. The rejections first allege that "administration of the compound (e.g. 9-cis retinal, 9-cis-10-F-retinal as addressed with Asato) intrinsically will have the same effect" (see Adv. Action of Dec. 2, 2010). This is clearly the improper *per se* test because it only asserts that "[a] known compound may suggest its homolog, analog, or isomer…."

The next allegation is that "certain [analogue] forms such as the 10-fluororetinal behaves very similarly to the parent retinal in all isomers, such as the 9-cis retinal … to yield stable pigments [with non-P23H opsin] (demonstrating functional equivalence of the 9-cis 10-fluorinated retinal analog to the parent 9-cis retinal)"[18]. But this "functional equivalence" is incorrect because the relevant functionality is binding to P23H mutant opsin. Therefore, this allegation improperly relies upon a property different from that needed in the claimed invention.

Additionally, and as Applicants previously explained,[19] binding to non-P23H (wildtype) opsin does **not** provide motivation or an expectation to achieve the claimed invention because the claimed methods are based on binding to P23H mutant opsin to prevent its aggregation and aid its folding. This error is also indicated by evidence with 11-*cis*-retinal, which is known to bind non-P23H (wildtype) opsin to form pigment, but under endogenous, physiological conditions is unable to prevent autosomal dominant RP in human subjects due to P23H mutant opsin.

Like the negative results discussed in Chapple et al. with respect to "cytoplasmic chaperones," the remaining rejections selectively ignore the evidence regarding 11-*cis*-retinal. Instead, the rejections allege that "Chapple addresses that chaperones can be utilized to manipulate the folding of normal (wild type) and mutant rhodopsin wherein there is an express teaching for chaperones for both normal (wild-type) and mutant rhodopsin with a reasonable expectation of success" (see Adv. Action of Dec. 2, 2010). But this allegation omits the negative results for "cytoplasmic chaperones" in Chapple et al. to incorrectly suggest that generally,

---

[16] *Takeda Chemical Industries, Ltd. V. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed Cir. 2007), quoting *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995), citing *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992), *In re Dillon*, 919 F.2d 688 (Fed. Cir. 1990) (*en banc*), *In re Grabiak*, 769 F.2d 729 (Fed. Cir. 1985), and *In re Lalu*, 747 F.2d 703 (Fed Cir. 1984).
[17] *Id.*
[18] (see Adv. Action of Dec. 2, 2010)
[19] See response filed November 19, 2010, page 8, last paragraph, and page 9, first paragraph.

a "chaperone" can positively affect the folding of normal rhodopsin or improve the misfolding of mutant rhodopsin. This allegation is improper (and based on faulty logic as explained above), and so it is clear that the rejections lack both the required motivation to use 9-*cis*-10-F-retinal ***and*** an expectation of success in using 9-*cis*-10-F-retinal.

V. Concluding Comments

In light of the foregoing, Applicants respectfully submit that there is no basis to conclude that a person of ordinary skill in the art, provided with the two cited documents, would have found it "obvious" to use 9-*cis*-10-F-retinal to bind P23H mutant opsin and prevent its aggregation in a manner that treats the human disease of RP caused by P23H mutant opsin.

This conclusion is not altered by the inclusion of the documents by Grant et al. ("Treatable forms of Retinitis Pigmentosa with systemic neurological disorders") and/or Lang et al. ("Ocular drug delivery conventional ocular formulations") and/or Geroski et al. ("Drug delivery for posterior segment eye disease").

Therefore, the remaining rejections are misplaced and may be properly withdrawn.

Conclusion

In light of the foregoing, Applicants respectfully submit that the claims are allowable and urge early indication to that effect. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at number below.

Respectfully submitted,

/kawai lau/
(Electronic Signature)
Kawai Lau, Ph.D.
Reg. No. 44,461

PATENTIQUE PLLC
PO Box 50368
Bellevue, Washington 98015
Tel: 425-228-0818
Fax: 425-228-8192